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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,905	12/10/2003	Nandan P. Koppiker	PC10332C	5794

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,905	KOPPIKER ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 17-34 ARE PRESENTED FOR EXAMINATION

Applicants' "Preliminary (sic) Amendment", Supplemental Information Disclosure Statement and Supplemental Application Data Sheet filed March 9, 2006 have been received and entered into the application.

Initially, Applicants are advised that the present Examiner is now the Examiner who began prosecution of the present application. Due to an absence from the Office, Examiner Leslie Royds prepared the previous Office action in the stead of the present Examiner. The present Examiner will continue prosecution of the instant application.

As per the above referenced amendment, claim 29 has been amended. Also, as reflected by the attached, completed copy of the form conforming to form PTO-FB-A820, (1 sheet), the Examiner has considered the references cited by Applicants.

In view of the Supplemental Application Data Sheet, which includes the mailing address for Eliot Forster, the objection to the Oath/Declaration, as set forth in the previous Office action dated September 8, 2005 at page 3, is *withdrawn*. Also, in light of the amendment to claim 29, the objection thereto, as set forth in the previous Office action at page 4, is *withdrawn*.

Claim Rejection - 35 USC § 103

Claims 17-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. (U.S. Patent No. 6,166,219), in view of Ellis et al. (WO 94/28902), Singh (WO 98/03167), Bueno et al. (U.S. Patent No. 6,127,418) and Stedman's Medical Dictionary, (herein after "Stedman's"), each of record, for the reasons of record as set forth in the previous Office action, which reasons are here incorporated by reference.

Applicants' remarks at pages 5-14 have been carefully considered, but fail to persuade the Examiner of error in the determination of obviousness.

In particular, Applicants have opined that the Examiner has failed to meet the burden of establishing a *prima facie* case of obviousness, (amendment at page 9). In support of this opinion, Applicants remark that "Quite simply there is nothing in the Yamasaki et al. reference that links a cGMP-PDE-V mechanism with the treatment of diabetic neuropathy.", (amendment at page 9). The Examiner does not agree with Applicants' assessment of the previously set forth rejection or the Yamasaki et al. reference. Contrary to Applicants' opinion, the previously set forth rejection meets the requirements of 35 U.S.C. § 103 for the very reasons set forth in the previous Office action at pages 4-8. In particular, as noted in MPEP § 2141, determination of obviousness under 35 U.S.C. § 103(c) requires that four factual inquiries be made: (A) determining the scope and contents of the prior art; (B) ascertaining the differences between the prior art and the claims in issue; (C) resolving the level of ordinary skill in the pertinent art; and (D) evaluating evidence of secondary considerations. These inquiries have been accomplished. With respect to inquiry (D), because no such evidence is of record, the previous Office action is equally silent in this respect.

Further, Yamasaki et al. not only expressly teaches the treatment of diabetic neuropathy at col. 35, lines 49-50, but further expressly teach that such neuropathy may be treated "***based on*** their [the disclosed benzimidazole compounds] cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity and antiallergic activity", (emphasis added; col. 35, lines 52-55). This teaching is clear, exact and unequivocally speaks to the contrary of Applicants' opinion.

While Applicants have taken the position that a *prima facie* case of obviousness has not been made, Applicants have nevertheless offered additional arguments against the propriety of the present rejection.

Bridging pages 9-10 of their amendment, Applicants apparently take the position that because a number of other conditions are taught by Yamasaki et al., there is no motivation to employ the presently claimed, specific PDE5 inhibitors for the purposes taught by Yamasaki et al. This position is apparently founded on the faulty premise that Yamasaki et al. do not disclose a relationship between cGMP-PDE-V mechanism with the treatment of diabetic neuropathy. As noted above, Yamasaki et al. most certainly does and from their disclosure, one of ordinary skill in the art would have recognized that any compound possessing the ability to inhibit cGMP-PDE-V could also be used and could provide the same ultimate therapeutic effect.

As to the number of conditions taught by Yamasaki et al., Applicants apparently believe that in some way the comprehensiveness of the disclosure of the patentees distracts from the teaching of a specifically disclosed disease/condition. That is, Applicants have remarked "Specifically, in the passage, col. 1, lines 14-44 certain benzimidazole derivatives are suggested for preventing and treating a plethora of about five dozen diseases/conditions. While one of the disease/condition listed is diabetic neuropathy there is quite simply no motivation from this passage to utilize a cGMP-PDE-V inhibitor for the treatment of diabetic neuropathy. The passage simply does not mention the cGMP-PDE-V mechanism."(amendment at page 10). Initially, the Examiner notes that the passage relied on by Applicants, i.e., col. 1, lines 14-44, was not relied on for the teaching which Applicants cannot locate. Rather, col. 35, lines 22-55 was specifically cited for this purpose, (see the previous Office action at page 5, lines 6-7).

Secondly, the comprehensiveness of the references teaching does not diminish the propriety of the present rejection. Diabetic neuropathy is clearly and unequivocally set forth. The Examiner is guided in his opinion by MPEP § 2131.02 under the heading "A Reference That Clearly Names The Claimed Species Anticipates The Claim No Matter How Many Other Species Are Named", (emphasis added) where it is set forth :"A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that 'the tenth edition of the Merck Index **lists ten thousand compounds**. In our view, **each and every one of those compounds is described**' as that term is used in 35 U.S.C. § 102(a), in that publication.'). Id. at 1718. See also *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982)", (emphasis added). Accordingly, Applicants' position is without merit or germane to the instant issue of obviousness.

The remaining arguments at pages 10 and the first paragraph of page 11 of the amendment are echoes of the above position. In response thereto, the Examiner relies on the above stated response.

At page 11, second paragraph, Applicants' have asserted that the present rejection is based on the improper standard of 'obvious to try'. The Examiner agrees with Applicants that 'obvious to try' is not the standard for obviousness which is precisely why the Examiner has not

based the instant conclusion of obvious thereon. Rather, the Examiner believes that what is claimed is what would have been "obvious to do".

In further response thereto, the Examiner looks to MPEP § 2145(X)(B), wherein it is stated: "'The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.' *In re O 'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)".

Here, the differences between the claimed subject matter and that of the prior art are not seen to rise to a situation where there are numerous possible choices, (see MPEP § 2131.02 relied on above) or where there is a new technology to explore. The art relied on, as well as the Examiner's assessment of such art, makes it clear that it would have been "obvious to do" what Applicant is claiming. The treatment of diabetic neuropathy, as well as any other of the clearly named diseases/conditions would have been obvious because such diseases/conditions are clearly named by the patentees. Also, because it is clearly disclosed that the compounds may be used based on the cGMP-PDE-V mechanism of action, it cannot be agreed, as urged by Applicants at page 12 of their amendment, that such amounts to "an invitation to 'explore a new technology or general approach that seemed to be a promising filed of experimentation, where the prior art

gave only general guidance as to the particular form of the claimed invention or how to achieve it.'". The teachings of Yamasaki et al are clear in this respect and direct the artisan, not to try, but to do with a reasonable expectation of success.

Applicants have set forth that the artisan would not have been imbued with a reasonable expectation of success, even if the art is, *arguendo*, viewed as providing a suggestion, In support of this position, Applicants have repeated their previous position that the Yamasaki reference only provides an invitation to experiment, "i.e., to perhaps making testing PDEV inhibitors more obvious to try, which again is manifestly not the proper standard for patentability"(see Applicants' amendment at page 13, first paragraph). However, insofar as the teachings of Yamasaki et al. are clear and would have been understood by one of ordinary skill in the art to use PDEV inhibitors for the purposes taught therein, it is maintained that the teachings of the reference are sufficient to base a proper conclusion of obviousness upon.

Applicants have also argued that rather than *In re Kerkhoven, In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987) is controlling. Here, however, unlike in *Geiger*, the reference was not as specifically detailed as Yamasaki et al. Short of anticipating the use of the claimed PDEV inhibitor, it is believed that the clear teaching of "***based on*** their [the disclosed benzimidazole compounds] cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity and antiallergic activity", (emphasis added; col. 35, lines 52-55) provides one of ordinary skill in the art with the reasonable expectation and motivation to employ other compounds possessing the same function and to reasonably expect the same results to occur as in Yamasaki et al. Further supporting the position of the Examiner is the MPEP at § 2144.06 where "Art

Recognized Equivalence for the Same Purpose" is discussed, and in particular, the "substituting equivalents known for the same purpose". The present rejection is fully consistent therewith and therefore the Examiner is compelled to maintain the rejection to be proper.

Applicants have also urged that an alpha 2 delta compound ligand and a PDE V inhibitor are different drugs used for different purposes functioning by different mechanisms (which further confounds the ability to guess at their effects if combined), (Applicants' amendment at page 13). The fact that different drugs are involved in the presently claimed subject matter is not seen as confounding. In the primary reference, Yamasaki et al. makes use of an astronomical number of "different" compounds, i.e., benzimidazole derivatives which are, in relation to each other, "different", and does so successfully. Also, it is not seen that the alpha 2 delta compound ligand (i.e., gabapentin or pregablin) and the PDEV inhibitors have different functions. They were both well known in the art to function as treatments for diabetic neuropathies. Finally, that two more compounds, used together, may have different mechanisms of action is not very impressive of an argument against such use because if this were true, than it would have to be the case that no two or more drugs could be used in combination with each other unless they each possessed the same mechanism of action.

At the final paragraph of page 13 of their amendment, Applicants have urged that the Examiner's rejection includes reasoning that "oversimplifies the combination of pharmaceutical agents". To the contrary of Applicants' position, it is believed that Applicants are overcomplicating the combination of the present active agents. The Examiner's position is not founded on the premise that it would have been obvious to combine any and all active agents in order to form a third composition that would be useful for the same purpose as each of the

individual actives. Rather, it merely has been reasoned that given (i) known compounds acting as cGMP PDE5 inhibitors and (ii) gabapentin and/or pregablin are all known to be useful for the same function, i.e., treating diabetic neuropathy, one of ordinary skill in the art would have been motivated to combine such compounds to form a third composition that is also useful for treating diabetic neuropathy.

In support of their apparent position that it is unusual and incredibly complex of a notion to combine active agents, Applicants have offered that such a combining action should be counterbalanced against the possibility of improved patient compliance and there are many reasons why those skilled in the art would not pursue a particular combination. The specific example identified by Applicants is the combination drug "PHEN-PHEN", i.e., a combination of phentermine and fenfluramine that was found to produce dangerous effects in some patients.

The Examiner cannot accept Applicants' position, which is set forth through pages 13-14 of their amendment, because to do so would be engaging in the logical fallacy of generalizing from the particular. As could be gleaned from any textbook or other comprehensive reference dealing with drugs and their actions, contraindications and possible side effects are common in the medical arts. In the face thereof, there still remains the act of administering active agents with known side effects and possible drug interactions for the purpose of treating individuals in need thereof. It is in the skill on the art to be aware of such possibilities and to proceed with due caution. Applicants would seem to have the Examiner believe that because side effects or drug interactions were possible for a given drug or combination of drugs, then one of ordinary skill in the art would never go forward and provide therapy to a patient in need thereof. The Examiner is aware that if the art were to teach away from a specific combination of agents, then such speaks

against a proper conclusion of obviousness. Here, however, Applicants have offered no evidence that such a teaching exists for a combination of a cGMP PDE5 inhibitor and gabapentin and/or pregablin. Hypothetical teachings away simply do not serve the place of an actual contraindication to a particular combination of active agents. That is, the *possibility* that the presently claimed combination of actives *could* have dangerous effects is not sufficient. The Examiner could equally take the position, and support such a position with a significant number of examples, in both the patent and non-patent literature, where drug combinations are taught and which have a favorable benefit-to-risk profile. In an effort not to crowd the present record with such references readily available to those having an interest therein, such references have not been cited by the Examiner. Therefore, for the above reasons this point of Applicants cannot be afforded the significance urged.

Accordingly, for the above reasons, it is maintained that the present rejection is proper and is therefor maintained.

None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

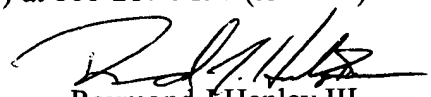
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Raymond J Henley III
Primary Examiner
Art Unit 1614

April 6, 2006